Royal Free London NHS
NHS Foundation Trust
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FULL/LONG TITLE OF THE STUDY
Path Active Multicentre Randomised Controlled Trial

SHORT STUDY TITLE / ACRONYM
PAM RCT

PROTOCOL VERSION NUMBER AND DATE
V1.4 – 11.06.2024

RESEARCH REFERENCE NUMBERS

IRAS Number:	326601
SPONSOR Number:	WWPP2.001
REC Number:	23/EE/0080

CHIEF INVESTIGATORS (CI):

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SPONSOR: Walk With Path

Representative of the Sponsor:

Miss Lise Pape,
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Funding Source: SBRI Healthcare Selection Panel. Ref SBRIH22P2006

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Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorisation from Royal Free London's R&D Office or its affiliates.

SIGNATURE PAGE

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Chief Investigator Declaration

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the approved protocol, GCP, the Data Protection Act (2018), the Trust's Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care (Last updated on 6 September 2023), the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the procedure identified as: SOP029 'Applying for Royal Free Sponsorship' and is intended for use at UK sites only**.**

For and on behalf of the Study Sponsor:

Signature: Date: ..../..../....
....

Name (please print):
.....

Position: .....

Chief Investigator: Richard Leigh
Chief Investigator Site: Royal Free London NHS Foundation Trust Date:
……/……/……

Signature: .....

Name: (please print):
Richard Leigh.....

Acknowledgements and Protocol contributories

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Chief Investigator	Richard Leigh (Consultant Podiatrist RFH, visiting professor PSMU)
Study Co-ordinator/Manager	N/A
Sponsor	Walk With Path
Funder(s)	SBRI
Key Protocol Contributors	Miss Lise Pape, Walk With Path Head Office, 54 Sun Street, Waltham Abbey, Essex, UK EN9 1EJ lise@walkwithpath.com +44 7976842669
Committees	RFL Trials Feasibility Committee

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1.0 LIST OF ABBREVIATIONS/GLOSSARY OF TERMS

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ISF	Investigator Site File
MDFT	Multidisciplinary Footcare Team
REC	Research Ethics Committee
RFL	Royal Free London NHS Foundation Trust
SOP	Standard Operating Procedure

2.0 ROLES AND RESPONSIBILITIES

CHIEF INVESTIGATOR (CI):

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3.0 STUDY SUMMARY

Official title:	Path Active; A multicentre randomised controlled trial
Brief title /Acronym:	PAM RCT
Sponsor reference number:	WWPP2.002
Public database trial ID:	TBC
Research Question	To evaluate the effectiveness of Path Active™ in people with diabetes who are at 'high risk' of foot ulceration.
Study design	Multicentre effectiveness randomised controlled trial
Eligibility criteria:	***Inclusion criteria:*** - Participant able to give informed consent. - Age >18 at the time of consent. - Diagnosis of Type 1 or Type 2 Diabetes. - Both Feet Intact (no ulceration). - Participant understands and is willing to participate and can comply with the follow-up regime. - Participant diabetes foot Risk Stratification as 'High Risk'. - Ability to walk independently for > 100 metres i.e without use of wheelchair, walking stick or personal assistance. - Participant able and willing to wear suitable footwear. - Must own a mobile phone and be willing to upload WWP app.
	Exclusion Criteria: - Either foot has less than 2 arterial vessel run-off on Doppler. - Poor visual acuity ie registered blind, unless supported by carer. - Current participation in another clinical investigation of a medical device or a drug; or participation in such a study within 30 days prior to study enrolment. - Body Mass Index (BMI) >40. - Active osteomyelitis (bone infection) suspected or diagnosed. - Active Charcots neuroarthropathy. - Participant has bespoke contact insoles and footwear. - Participant is unable to use 'medium' or 'large' insoles due to foot size eg. small or extra large feet. - Participant has a pacemaker.

	- Participant is pregnant.
Anticipated start date	2nd April 2024
Anticipated end date	31st March 2025
Target number of participants	120
Primary aim(s)	The primary objective of this clinical investigation is to evaluate the effectiveness of Path Active™ in people with diabetes who are at 'high risk' of foot ulceration.
Secondary aim(s)	To establish the 'carbon footprint' of Path Active in different geographies.
Sources of funding	SBRI Healthcare Selection Panel. Ref SBRIH22P2006
Sponsor	Walk With Path
Contact name	***Sponsor representative:*** Miss Lise Pape, Walk With Path Head Office, 54 Sun Street, Waltham Abbey, Essex, UK EN9 1EJ Phone: +44 7976842669 Email: lise@walkwithpath.com ***Chief Investigator:*** Prof Richard Leigh, Podiatry Dept, Royal Free London NHS Foundation Trust, Royal Free Hospital, Pond Street, Hampstead, London, NW3 2QG **Phone:** 020 7830 2749 **Email:** richardleigh1@nhs.net

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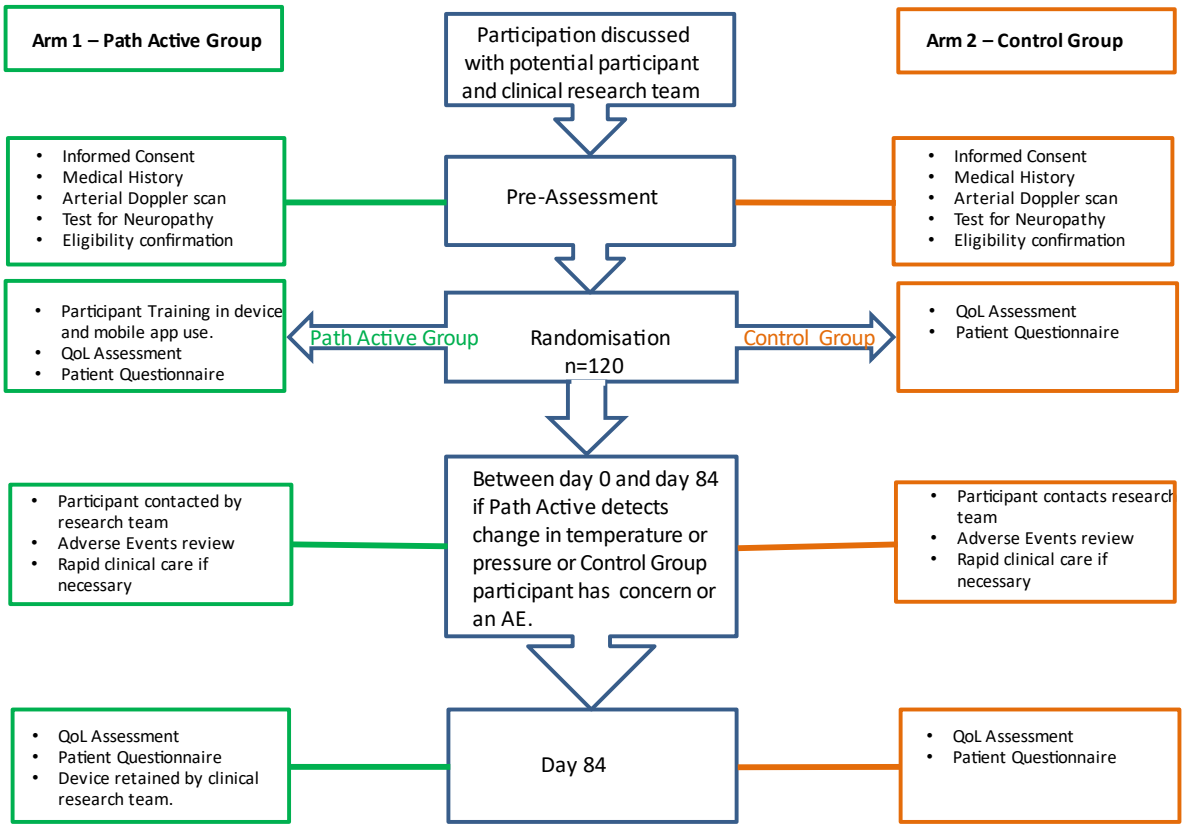
4.0 STUDY FLOW CHART



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5.0 INTRODUCTION

5.1 BACKGROUND

More than 4.9M people have been diagnosed with diabetes (DM) in the UK, and up to 25% (1.2M) will develop a Diabetic Foot Ulcer (DFU) in their lifetimes. 15-20% of DFUs lead to amputations which are followed by significantly increased mortality. The cost to taxpayers is enormous (Kerr 2019), consuming 1% of NHS budget annually.

The current method of providing periodic foot checks is inadequate, with the chance of recurrence of an ulcer being 40% in the first year, rising to almost 100% over 10 years (Armstrong 2017). Individuals at high risk of DFU go to clinic to have their feet checked at least once a month. This can be highly disruptive to their everyday lives. Furthermore, there is considerable environmental cost of patient travel and if a DFU occurs single-use consumables for treatment such as dressings, bandages, scalpels, blood tests, cultures for microbiology , etc.

5.2 RATIONALE

Foot ulceration and infection is a major factor leading to morbidity (amputation) and mortality. There are multiple comorbidities which can lead to foot ulceration and infection such as peripheral arterial disease and diabetes. The estimated cost of foot care in England for people with diabetes and foot ulceration alone is £1billion (Kerr 2019) with around 9000 amputations a year (one an hour). Many amputations occur due to ulceration leading to infection.

Path Active is an advanced at-home foot health monitoring system that combines unique patented, sensor-rich insoles and patient-adapted machine learning to prevent DFUs. Path Active does this by accurately mapping and measuring a person's foot pressure and temperature distribution to calculate increasing risk of foot ulceration and allow users to take appropriate actions to reduce their DFU risk. For patients, a highly-visual dedicated UI (User Interface - app & web portal), with embedded behavioural science-led 'nudge methodology', supports and encourages them to offload (rest) their feet to prevent DFU development and liaise remotely with their clinician. These systems have been shown to reduce DFU recurrence with the single modality of pressure measurement (Chatwin 2021; Abbott 2019). Additionally, Path Feel measures temperature change as a precursor to foot disease as well as pressure and reduces the need for frequency of clinic visits by providing at-home monitoring. Alerts are also captured on a clinical dashboard by the patient's clinical team which will alert them to potential foot problems and so they can contact the patient and provide rapid clinical care when required.

From a healthcare professional's perspective, the platform provides a major opportunity to save time and personalise care, focusing on only those patients who need help.

6.0 RESEARCH QUESTIONS

- Is Path Active as effective as regular routine podiatry review in foot ulcer prevention?
- Does using Path Active improve participant QoL?
- Are there any suggestions from participants to improve the device/app?
- Will preventing foot ulceration reduce NHSE carbon footprint?

6.1 PRIMARY AIM

The primary objective of this clinical investigation is to evaluate the effectiveness of Path Active™ in people with diabetes who are at 'high risk' of foot ulceration compared to regular routine podiatry clinical review.

6.2 SECONDARY AIMS

To model the carbon dioxide reduction that mat occur if ulceration and the need for ulcer treatment is prevented, in differing UK geographies.

7.0 TRIAL DESIGN

7.1 METHOD

Study setting
Participants who have been assessed as having a 'high risk' of foot ulceration will be recruited from Community Foot Protection Teams in 4 sites across the UK. Participants will be recruited to the study to a maximum total of 120 (30 at each site) who have completed the study. The number of recruits required is based on a power calculation for the study at the 95% confidence interval.
The study is anticipated to run for 12 months.

Procedure
Potential participants will be approached to participate during routine review by the Community Foot Protection Teams and consented by them for the study. All participants will be screened at pre-assessment by the Community Foot Protection Teams.

Following completion of informed consent the participant will have;

- Medical History
- Arterial Doppler scan

- Test for Neuropathy
- Eligibility confirmation
- EuroQoL Assessment (EQ-5D-5L)
- Patient Questionnaire
- Randomised to 'Path Active Group' or 'Control Group' using computer randomisation.

If the participant is randomised to use the device in the 'Path Active Group';

- Participant Training in device and mobile app use (Appendix 1).

If there is an alert from Path Active app the participant will be asked to reduce walking and rest their feet. If the alert continues and activates the clinical dashboard, patients will be contacted to attend clinic for review.

If the participant is not randomised to use the device in the 'Control Group', they will continue with their regular podiatry clinical reviews with the Community Foot Protection Team who will provide their standard of care.

Day 84 (week 12). At the end of study;

- EuroQoL Assessment (EQ-5D-5L)
- Patient Questionnaire

If the participant is randomised to use the device;

- Device retained by clinical research team.

8.0 PARTICIPANT SELECTION CRITERIA

Interested participants thought to be appropriate for the study will be approached by the local Community Foot Protection Team. Following informed consent, participants will be assigned a subject ID and their status checked that they satisfy inclusion and exclusion criteria prior to admitting them to the trial. Participants will be excluded if they do not satisfy inclusion and/or exclusion criteria.

8.1 INCLUSION CRITERIA

- Participant able to give informed consent.
- Age >18 at the time of consent.
- Diagnosis of Type 1 or Type 2 Diabetes.
- Both Feet Intact (no ulceration).
- Participant understands and is willing to participate and can comply with the follow-up regime.
- Participant diabetes foot Risk Stratification as 'High Risk' as in Frame (2021) Scotland/England https://www.diabetesframe.org/

- Ability to walk independently for > 100 metres i.e without use of wheelchair, walking stick or personal assistance.
- Participant able and willing to wear suitable footwear.
- Must own a mobile phone and be willing to upload WWP app.

8.2 EXCLUSION CRITERIA

- Either foot has less than 2 arterial vessel run-off on Doppler.
- Poor visual acuity ie registered blind, unless supported by carer.
- Current participation in another clinical investigation of a medical device or a drug; or participation in such a study within 30 days prior to study enrolment.
- Body Mass Index (BMI) >40.
- Participant has bespoke contact insoles and footwear.
- Participant is unable to use 'medium' or 'large' insoles due to foot size eg. small or extra large feet.
- Participant has a pacemaker.
- Participant is pregnant.

8.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the study. If participants withdraw the data already collected will be anonymously utilised, but no further data will be collected.

9.0 PARTICIPANT RECRUITMENT PROCESS

The study will only commence once evidence of the following approval/essential documents are in place:

1. The main REC approval (if applicable),
2. HRA approval
3. Final sponsorship and host site confirmation of capacity and capability

All participants who wish to enter the study will be approached by the local Community Foot Protection Team and written consent taken. Potential participants will have the opportunity to ask any questions they have prior to giving consent. Patient information sheets will be available as part of the consenting process.

10.0 STUDY PROCEDURES

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10.1 INFORMED CONSENT

Informed consent from the participant will be obtained in clinic following provision of written information to the potential participant. Any queries the potential participant may have should be addressed by delegated and trained members of the local study team.

The information supplied to the potential participant will include a statement that they are under no obligation to enter the trial and that they can withdraw at any time, without having to give a reason.

10.2 SCHEDULE OF EVENTS

Path Active	**Screening (Pre-enrolment assessment)**	**Active phase 0 - 84 days.**			**Final visit**
Visit No:	1	2		3 due to alert/concern	4
Form Number	F01, F02, F03, F04, F05	F06	F06	F07 (F09)	F08
TIMING	Pre-Assessment	Day 0 **Path Active Group**	Day 0 **Control Group**	When required	Week 12 (Day 84)
Window of flexibility for timing of visits:	- 7 days			1 day	+7 days
Randomisation		**Randomisation**			
Informed Consent	X				
Medical History or change to medication	X			X	
Eligibility confirmation	X			X	
Feet Assessment Neuropathy	X				
Feet Assessment Vascular Doppler	X			X	
Adverse Events review (unless reported prior to visit)				X	X
Questionnaire		X	X		X

EQ-5D-5L		X	X		X
Path Active insole fitting		X			
Daily Dashboard Review by Clinical Team		X			

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11.0 ADVERSE AND SERIOUS ADVERSE EVENTS

11.1 GENERAL DEFINITIONS

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical trial subject which does not necessarily have a causal relationship with the device/procedure.

A Serious Adverse Event (SAE) is an untoward occurrence that:
- Is fatal
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

Medical and scientific judgement must be exercised in deciding whether an event is serious. There characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above. All potential intervention-related AEs (such as falls and consequent injuries related to wearing the insoles) will be investigated and subject to expedited reporting to the REC.

12.0 OPERATIONAL DEFINITIONS OF (S)AES

12.0.1 Expected (S)AEs - Not Reportable

This is a trial in a patient population with high levels of morbidity and co-morbid diseases and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected.

In recognition of this, events fulfilling the definition of an adverse event or serious adverse events will not be reported in this study unless they are classified as ‘related’.

12.0.2 Expected (S)AEs - Standard Reporting

The following AEs and SAEs are expected within the patient study population and will be reported from randomization to trial completion on standard Case Report Forms (CRFs) where the device is not a factor in the event:

• Death
• Hospital admission

• Institutionalisation

As these events are expected within the study population they will not be subject to expedited reporting to the main REC.

12.2 RESPONSIBILITIES

Community Foot Protection Team:

- Checking for SAEs when participants attend following an alert from Path Active or there is concern from either Path Active Group or Control Group participants
- Judgement in assigning:
  - Seriousness
  - Relatedness
  - Expectedness
- To ensure all SAEs are recorded and reported to the CI within 24 hours of becoming aware and to provide further follow-up information as soon as available.

CI or delegate:

- Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review.
- Review all events assessed as Related / Unexpected in the opinion of the CI prior to reporting to the main REC.

13.0 DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

The study will abide by the Caldicott Principles, the Data Protection Act 2018 and General Data Protection Regulations for reviewing and managing personal data. All data will be kept confidential, stored appropriately and anonymised in as far as is possible. As with standard clinical practice, confidentiality may need to be broken if participants or others are at serious risk. This will be explained to participants when they consent to participate in the project.

All participants will be given a study number, allocated sequentially by the clinical team. The study will comply with the General Data Protection Regulation (GDPR) which requires data to be anonymised as soon as it is practical to do so. Data will be analysed anonymously.

The CRF will not bear the subject's name or other directly identifiable data. The subject's trial Identification Number (ID) only, will be used for identification. Participant identifiable information (e.g. the signed consent form) will be kept with the study number securely by local study teams, in case of

the unlikely requirement for breaking confidentiality. This list matching identifiable participant information and study numbers will not be kept outside of the local study team.

13.2 DATA COLLECTION

Data Collection will be via a paper CRF complied by the study team. Any data eg spreadsheet of participants, will be processed via NHS IT systems and stored in secure network folders.

13.3 DATA HANDLING AND ANALYSIS

CRFs will be completed on paper. Data collected will be stored on secure server and in excel files.

Study documents (paper and electronic) containing details of demographic data, documentation of inclusion and exclusion criteria, and medical history will be retained for a period of 5 years following the end of the study

13.4 TRANSFERRING/TRANSPORTING DATA

If data transfer is required, it will only be transferred via secure nhs.net email and will be anonymised.

14.0 ARCHIVING

During the course of research, all central records are the responsibility of the Principle Investigators and must be kept in secure conditions. The PIs will have responsibility for storage of consent forms and a list of patient identifiers with study numbers. The PIs will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement.

The trial essential documents along with the trial database will be archived in accordance with the sponsor. The agreed archiving period for this trial will be 5 years.

15.0 ENDPOINT DESIGN

15. 1 ENDPOINTS

15.1.1 PRIMARY ENDPOINTS

- Day 84 all participants will be asked to complete a health-related quality of life questionnaire and a questionnaire regarding patient experience and, for the Path Active Group, use of the device and suggested improvements with the device and associated 'app'.
- To model any reduction in carbon footprint due to ulcer prevention.

15.1.2 SECONDARY ENDPOINTS

- At end of study review all alerts from Path Active and responses to the alerts. Was ulceration prevented? Were there any conflicting outcomes from device use?

15.2 ANALYSIS PLANS

15.2.1 PRIMARY ENDPOINT ANALYSIS

Day 84; Data will be analysed to determine the effectiveness of 'Path Active' compared with standard podiatry review.
Questionnaires will be reviewed for QoL outcomes and patient experience.

15.2.2 SECONDARY ENDPOINT ANALYSIS

Day 84; Alerts from Path Active will be analysed to assess a base level of sensitivity and specificity.

16.0 DIRECT ACCESS TO SOURCE DATA

The Community Foot Protection Teams will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will be asked to consent to provide access to their medical records.

17.0 ETHICS AND GOVERNANCE REQUIREMENTS

Before Community Foot Protection Teams can enrol patients into the trial, the Chief Investigator must ensure written permission to proceed has been granted by that Trust Research & Development Department (R&D).
The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA) where applicable.

The Principle Investigators will be provided (via the Sponsor) with file indexes TMF Index RLFRDDOC0013 and ISF index RFLRDOC0003 for use with SOP019 'Preparation and Maintenance of the Site File – and SOP054 'Preparation and Maintenance of the Trial Master File'. The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial. The sponsor can provide an End of study Report template RFLRDDOC0005

17.1 DEFINITION OF THE END OF TRIAL

The last patient completing day 84 of the trial.

17.2 ANNUAL PROGRESS REPORTS (APRs)

The Chief Investigator will prepare the APR in accordance with the RFL R&D Office's SOP 056 'Annual Progress Reports'. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

17.3 PROTOCOL COMPLIANCE

Any Protocol Deviations, Violations will be documented using the deviation reporting form (Form 10 WWPP2 Protocol Deviation) and processed according to R&D OFFICE SOP 032

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a violation of the protocol or a breach of Data protection.

18.0 FINANCE

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SBRI Healthcare Selection Panel. Ref SBRIH22P2006

19.0 PEER REVIEW

The documents have been reviewed by the study team, Patient group (PPIE), Sponsor (WWP) and Royal Free Hospital R&D Committee.

20.0 PUBLIC AND PARTICIPANT INVOLVMENT

Patients have completed questionnaires regarding the study and use of the device. Also a patient group at the Royal Free Hospital have discussed the study and use of the device. Both questionnaires and patient group discussion where favourable of the device and the study.

21.0 INDEMNITY

Normal NHS-indemnity processes apply, as documented in HSG(96)48. This covers negligent harm during the study, and covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. The sponsoring company will provide indemnity for the management of the study via their liability insurance.

22.0 IP AND DEVELOPMENT POLICY

Intellectual property may be generated from this study and will remain the property of Walk With Path.

23.0 PUBLICATION AND DISSEMINATION POLICY

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”
All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.
To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication

prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

24.0 STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC

25.0 REFERENCES

Abbott CA, Chatwin KE, Foden P, Hasan AN, Sange C, Rajbhandari SM, Reddy PN, Vileikyte L, Bowling FL, Boulton AJM, Reeves ND. Innovative intelligent insole system reduces diabetic foot ulcer recurrence at plantar sites: a prospective, randomised, proof-of-concept study. Lancet Digit Health. 2019 Oct;1(6):e308-e318. doi: 10.1016/S2589-7500(19)30128-1. Epub 2019 Sep 26. PMID: 33323253.

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26.0 APPENDICIES

Appendix 1

Path Active Manual_v3.pptx (2).p